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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/677,495	10/03/2003	Chun L. Gao	8124.003.US	4565

7590 02/22/2007

James Remenick
Novak, Druce, Quigg & DeLuca
East Tower, Suite 400
1300 Eye Street, N.W.
Washington, DC 20005

EXAMINER	
SANG, HONG	
ART UNIT	**PAPER NUMBER**
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/22/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	**Application No.** 10/677,495	**Applicant(s)** GAO ET AL.	
	Examiner Hong Sang	**Art Unit** 1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20 and 38-53* is/are pending in the application.

4a) Of the above claim(s) *19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18, 20, and 38-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☒ Other: *Exhibits A and B*.

DETAILED ACTION

RE: Gao et al.

1. The examiner of your application in the PTO has changed. To aid in correlating of any papers for this application, all further correspondence regarding this application should be directed to Hong Sang, Art Unit: 1643.

2. Applicant's response filed on 12/15/06 is acknowledged. Claims 1-20 and 38-53 are pending. New claims 38-53 are added. Claims 21-37 are cancelled. Claims 1-3 and 20 are amended. Claim 19 is withdrawn from further consideration as being drawn to non-elected inventions.

3. Claims 1-18, 20 and 38-53 are under examination.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Objections Withdrawn

5. The objection to the abstract of the disclosure because there is an extra "a" in line 4 is withdrawn in view of applicants' amendment to the abstract.

6. The objection of claim 19 for being drawn to non-elected species of the invention is withdrawn in view of applicant's withdrawn the claim from further consideration.

Objections Maintained

7. The objection to the specification because applicants fail to update the status (pending, allowed, etc.) of all parent priority applications in the first line of the specification is maintained.

Applicants claimed the benefit of the prior-filed US provisional application no. 60/281,387 in the Oath/Declaration. The first line of the specification should be updated if applicant desires priority under 35 U.S.C. 1 19(e) based upon the provisional application no. 60/281,387.

Rejections Withdrawn

8. The rejection of claims 2, 3, and 20 under 35 U.S.C. 112, second paragraph, as being indefinite for the recitation "sensitivity is at least about 80% or greater" in claim 2, "sensitivity greater than 80%" in claim 20, line 15, "specificity is at least about 85% or greater" in claim 3 and "specificity greater than 85%" in claim 20, lines 15 and 16 is withdrawn in view of applicants' amendments to the claims.

9. The rejection of claims 1, 3-6, 11, 12, 14, and 18 under 35 U.S.C. §102(b) as being anticipated by Croce et al. (US Patent 5,674,682, patented October 7, 1997) is withdrawn in view of new grounds of rejection.

10. The rejection of claims 1, 4-6, 11, 13, 14, 16, and 18 under 35 U.S.C. §102(b) as being anticipated by Gao et al. (Urology 53: 714-721, 1999) is withdrawn in view of new grounds of rejection.

11. The rejection of claims 1-6, 11-18, and 20 under 35 U.S.C. §103(a) as being unpatentable over Croce et al. (US Patent 5,674,682, patented October 7, 1997) in view

of Edelstein et al. (WO 96/21042; international publication date 11 July 1996), and Tso et al. (WO 97/38313; international publication date 16 October 1997) is withdrawn in view of new grounds of rejection.

12. The rejection of claims 1, 3-12, 14, and 18, are rejected under 35 U.S.C. §103(a) as being unpatentable over Croce et al. (US Patent 5,674,682, patented October 7, 1997) in view of Terstappen et al. (US Patent 6,365,362, filed 12 February 1999) is withdrawn in view of new grounds of rejection.

13. The rejection of claims 1-6, 11-18, 20 under 35 U.S.C. §103(a) as being unpatentable over Gao et al. (Urology 53: 714-721, 1999) in view of Edelstein et al. (WO 96/21042; international publication date 11 July 1996) is withdrawn in view of new grounds of rejection.

14. The rejection of claims 1, 4-11, 13, 14, 16-18 under 35 U.S.C. §103(a) as being unpatentable over Gao et al. (Urology 53: 714-721, 1999) in view of Terstappen et al. (US Patent 6,365,362, filed 12 February 1999) is withdrawn in view of new grounds of rejection.

New Grounds of Rejections

15. Claims 1-18, 20 and new claims 38-53 are rejected under 35 U.S.C. §103(a) as being unpatentable over Gao et al. (Urology, 1999, 53: 714-721), in view of Terstappen

et al. (US Patent 6,365,362, effective filing date at least 2/12/1999), Croce et al. (US Patent 5,674,682, Date of Patent: 10/7/1997), Katz et al. (US Patent 5,840,494, Date of Patent 11/24/1998), and Tso et al. (WO 97/38313, international publication date: 10/16/1997).

Gao et al. disclose a method to detect PSA-expressing prostate cancer cells as low as one cell in 10 million lymphocytes (1 X 10^7), see Abstract, lines 6-8; page 715, right column, Determination of PCR Sensitivity section, lines 6 and 7). Gao et al. teach that using their PCR conditions, they could confidently detect LNCaP cells to lymphocytes in a ratio of 1 LNCaP cell per 10^7 lymphocytes (see page 715, right column, Determination of PCR Sensitivity section, lines 6 and 7). Gao et al. teach that of 85 patients undergoing radical prostatectomy, RT-PCR-PSA assays detected circulating prostate cells preoperatively in 27 patients (31.8%), and of the 22 controls, no patient was RT-PCR-PSA positive. Because none out of the 22 controls was RT-PCR-PSA positive, the false positive in Gao et al. is zero, indicating true positives/true positives plus false positives is 100%. Gao et al. teach that in 10 randomly selected cases, the RT-PCR product was confirmed as PSA by DNA sequencing (see abstract). Gao et al. disclose that of the 27 patients undergoing radical prostatectomy who were RT-PCT positive, 16 (59.3%) had organ-confined disease (see Table IV). Gao et al. disclose isolating PSA-expressing cells from 7ml of peripheral blood of patients (see page 715, 2nd paragraph, lines 14-16). Gao et al. disclose random hexamer primers, primers specific for PSA, and nested PCR primers, see page 715, last paragraph and page 716, 1st paragraph). Gao et al. teach the primers that contains sequences specific for exons of the PSA gene (see page 716, right column, line 12). Gao et al. disclose the preoperative serum PSA level of the patients (see Table III). While Gao et al. do not specifically disclose the biopsy for the patients, obtaining the information regarding the grade and clinical stage of the cancer (see table III) would require a step of biopsy. Gao et al. teach that limits of sensitivity of their RT-PCR assays in attempting to detect a very small number of circulating prostate cells in peripheral blood may account for differences in the results reported from different groups (see page 720, 2nd paragraph).

Gao et al. do not teach the claimed sensitivity such as 80%. Gao et al. do not teach the use of oligo-dT primers. Gao et al. do not teach the SEQ ID NO.3 and SEQ ID NO.4. Gao et al. do not teach isolating epithelial cells using immunological methods. However, these deficiencies are made up for by the teachings of Terstappen, Croce, Katz and Tso et al.

Terstappen et al. teach a method for detection and enrichment of prostate cancer specific cells from blood sample, said method comprises use of immunomagnetic beads (dynal magnetic beads) to isolate said cells (see column 8, lines 11-53). Terstappen et al. teach the use of antibodies to epithelial antigens such as anti-EpCAM to enrich or isolate epithelial cells (see column 10, lines 32-37 and Example 2). Terstappen et al. teach that an increase in circulating epithelial cells in the blood is correlatable with disease activity, in three patients with no detectable spread of the cancer, epithelial cells were found in 20 ml of the peripheral blood (see Example 5). Terstappen et al. teach detection of tumor cells in the blood of a patient with high PSA levels and a negative biopsy (see Example 8). Terstappen et al. teach that their assay can detect one epithelial cell or less in 1 ml of blood (see abstract).

Croce et al. disclose a method for detecting prostate cancer in a patient, wherein the method comprises isolating epithelial cells from a sample of blood from said patient, lysing epithelial cells and isolating nucleic acid, conducting RT-PCR on said isolated nucleic acid using a set of primers, Taq polymerase to synthesize cDNA, conducting PCR on said cDNA using PSA-specific primers and Taq polymerase and detecting amplified PSA gene (see column 3, lines 35-66; column 9, lines 15-67; column 10, lines 1-20). Croce et al. also disclose that the prostate cancer includes sub clinical stage, organ-confined prostate cancer in humans (Stages D0 and D1), see column 8, lines 56-64; column 11, lines 1-15. Croce et al. disclose that the blood sample comprises peripheral blood (see column 11, lines 2-4). Croce et al. disclose primers, for example SEQ ID NO: 9, that contain specific exons of the PSA gene which include instant claimed SEQ ID NO: 4 (see column 3, lines 56-66; column 12, lines 45-55, and sequence alignment Exhibit A). Croce et al. further disclose obtaining a blood sample of approximately 6 ml (see column 9, lines 15 and 16).

Katz et al. teach the use of oligo-dT primer in RT-PCR detection of mRNA encoding PSA in circulating cells expressing PSA (see column 2, lines 11-21 and 29-30).

Tso et al. teach a method for enriching rare cells in a fluid comprising the rare cells (that are preferably rare non-blood cells) and non-rare cells, and further identifying the rare cells (see page 3, lines 3-5 and 21-23). Tso et al. teach a PSA-specific probe (SEQ ID NO: 3) that comprises the instant SEQ ID NO: 3 (see sequence alignment Exhibit B, page 21, lines 2-5, 219-28; page 48, claims 11 and 13). Tso et al. teach that the probes can be used for PCR to identify or detect rare cancer cells (see page 20, lines 15-21).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to modify the method of Gao et al. to first enrich the tumor specific cells that are present in blood and then perform RT-PCR in view of the teachings of Terstappen et al. A person of ordinary skill in the art would have been motivated to modify the method of Gao et al. by incorporating the step of enriching tumor specific cells as taught by Terstappen et al. for the purpose of increasing the sensitivity of the method and reducing the background. One of ordinary skill in the art would have a reasonable expectation of success to do so because Terstappen et al. teach how to enrich prostate cancer cells in a sample of blood and Gao et al. teach how to detect PSA mRNA using RT-PCR. Moreover, it would have been obvious and one would have been motivated to use primers such as SEQ ID NOs.3 and 4 and oligo dT primers in the RT-PCR of Gao et al. because these primers have been well known and successfully used for detection of PSA mRNA as shown by the teachings of Croce, Katz and Tso et al. Therefore, the combination of the references teaches all the active steps of the claimed method. While the references do not specifically teach the claimed sensitivity i.e. 70% and 80%, because the method steps taught by the prior art appear to be the same as the instantly-claimed, by performing the same steps, one would expect to achieve the same sensitivity.

Conclusion

16. No claims are allowed.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hong Sang whose telephone number is (571) 272 8145. The examiner can normally be reached on 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry R. Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Hong Sang, Ph.D.
Art Unit 1643
Feb. 15, 2007

CHRISTOPHER H. YAEN
PRIMARY EXAMINER

Exhibit A

```
<!--StartFragment-->RESULT 1
US-08-358-782D-9
; Sequence 9, Application US/08358782D
; Patent No. 5674682
;  GENERAL INFORMATION:
;    APPLICANT:  Croce, Carlo
;    APPLICANT:  Gomella, Leonard
;    APPLICANT:  Mulholland, S. Grant
;    APPLICANT:  Moreno, Jose
;    APPLICANT:  Fischer, Rainer
;    TITLE OF INVENTION:  Methods of Detecting Micrometastasis of Prostate
;    NUMBER OF SEQUENCES:  14
;    CORRESPONDENCE ADDRESS:
;      ADDRESSEE:  Woodcock Washburn Kurtz Mackiewicz &
;      STREET:  One Liberty Place 46th. Floor
;      CITY:  Philadelphia
;      STATE:  PA
;      ZIP:  19103
;    COMPUTER READABLE FORM:
;      MEDIUM TYPE:  Floppy disk
;      COMPUTER:  IBM PC compatible
;      OPERATING SYSTEM:  PC-DOS/MS-DOS
;      SOFTWARE:  PatentIn Release #1.0, Version #1.25
;    CURRENT APPLICATION DATA:
;      APPLICATION NUMBER:  US/08/358,782D
;      FILING DATE:  15-DEC-1994
;      CLASSIFICATION:  435
;    ATTORNEY/AGENT INFORMATION:
;      NAME:  Beardell, Lori Y.
;      REGISTRATION NUMBER:  34,293
;      REFERENCE/DOCKET NUMBER:  TJU-1327
;    TELECOMMUNICATION INFORMATION:
;      TELEPHONE:  215-568-3100
;      TELEFAX:  215-568-3439
;  INFORMATION FOR SEQ ID NO:  9:
;    SEQUENCE CHARACTERISTICS:
;      LENGTH:  25 base pairs
;      TYPE:  nucleic acid
;      STRANDEDNESS:  single
;      TOPOLOGY:  linear
;    MOLECULE TYPE:  DNA (genomic)
;    HYPOTHETICAL:  NO
;    ANTI-SENSE:  NO
US-08-358-782D-9

  Query Match             90.5%;  Score 19;  DB 2;  Length 25;
  Best Local Similarity   100.0%;  Pred. No. 9.8;
  Matches   19;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CATCACCTGGCCTGAGGAA 19
              |||||||||||||||||||
Db          7 CATCACCTGGCCTGAGGAA 25

<!--EndFragment-->
```

Exhibit B

```
AAT89213
ID   AAT89213 standard; DNA; 60 BP.
XX
AC   AAT89213;
XX
DT   30-APR-1998  (first entry)
XX
DE   Prostrate specific antigen mRNA probe 4.
XX
KW   Prostrate specific antigen; PSA; probe; hybridisation; cancer; vaccines;
KW   ss.
XX
OS   Synthetic.
XX
PN   WO9738313-A1.
XX
PD   16-OCT-1997.
XX
PF   02-APR-1997;   97WO-US005586.
XX
PR   05-APR-1996;   96US-0014929P.
XX
PA   (UYJO ) UNIV JOHNS HOPKINS.
XX
PI   Tso POP,  Wang Z,  Lesko SA,  Nelson WG,  Partin AW;
XX
DR   WPI; 1997-512878/47.
XX
PT   Isolating rare cells by density gradient separation then negative
PT   selection - used for enriching prostatic cancer cells for diagnosis,
PT   staging and monitoring of disease.
XX
PS   Claim 13; Page 21; 63pp; English.
XX
CC   This sequence is a probe for prostate specific antigen (PSA),
CC   particularly useful for in situ hybridisation. The probe is used to
CC   detect the epithelial cells of prostatic cancer cells, via the detection
CC   of PSA and/or PSMA (prostate specific membrane antigen). The method is
CC   especially used to enrich prostatic cancer cells from blood, allowing
CC   detection and characterisation of these cells for diagnosis, staging and
CC   monitoring of disease. It can also be applied to the enrichment of liver,
CC   hepatoma, hepatocarcinoma or cancer cells in general
XX
SQ   Sequence 60 BP; 14 A; 18 C; 17 G; 11 T; 0 U; 0 Other;

  Query Match             100.0%;  Score 23;  DB 2;  Length 60;
  Best Local Similarity   100.0%;  Pred. No. 0.78;
  Matches   23;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CACTGCATCAGGAACAAAAGCGT 23
              |||||||||||||||||||||||
Db         17 CACTGCATCAGGAACAAAAGCGT 39
```